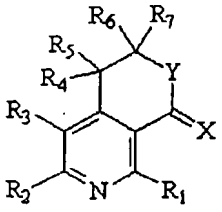
Additional Claims Amendment

What is claimed is:

1.(Newly Amended) A compound or pharmaceutically acceptable salt of the following formula 1,



(1)

wherein R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from the group consisting of a hydrogen atom, a halo, a cyano, a nitro, an acyl, a hydroxy, an amino, a C_1-C_6 low alkyl, a C_2-C_6 low alkenyl, a C_1-C_6 low alkoxy, a C_1-C_6 alkylthio, a C_1-C_{10} alkylamino, a C_4-C_9 cycloalkylamino, a C_4-C_9 heterocycloalkylamino, a C_1-C_{10} aralkylamino, an arylamino, an acylamino, a saturated heterocyclic, an acyloxy, a C_1-C_6 alkylsulfinyl, a C_1-C_6 alkylsulfonyl, a C_1-C_6 alkylsulfonylamino, an arylsulfinyl, an arylsulfonyl, an arylsulfonylamino, an aryl, a heteroaryl, a C_1-C_{10} aralkyl, a C_1-C_{10} heteroaralkyl, an aryloxy and a heteroaryloxy group; or R_1, R_2, R_3, R_4, R_5, R_6 and R_7 independently form a ring by binding with a neighboring substitution group;

X is an oxygen or sulfur atom;

Y is an oxygen atom or N-R_8, wherein R_8 is selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl, an acyl, an aryl, a heteroaryl, a C_1-C_{10} aralkyl and a C_1-C_{10} heteroaralkyl group; or forms a ring by binding with a

neighboring substitution group of R_6 or R_7;

said aryl group is selected from a phenyl, a naphthyl and a fused phenyl group;

said heteroaryl and saturated heterocyclic groups are a heterocyclic ring with a pentagonal or hexagonal shape having 1 to 3 heteroatoms selected from an oxygen, a nitrogen, and a sulfur atom; or a fused heterocyclic ring; and

said aryl and heteroaryl groups are such that 1 to 4 substitution groups selected from the group consisting of a halo, a hydroxy, a C_1-C_6 low alkyl, a C_1-C_6 low alkoxy, an amino, a cyano, a nitro, a carbonyl and a carboxyl group are substituted,

wherein said compound or pharmaceutically acceptable salt of the following formula 1 is not 6-methyl-3,4-dihydro-pyrano[3,4-c]pyridin-1-one, 5-vinyl-3,4-dihydro-pyrano[3,4-c]pyridin-1-one, 3-t-butyl-5,6,7,8-tetrahydro-[2,7]naphthyridin-8-one and (3S)-6,8-dimethyl-1-oxo-1,2,3,4-tetrahydro-[2,7]naphthyridine-3,5-dicarboxylic acid dimethyl ester

2. In claim 1, said X and Y are independently an oxygen atom.

3. In claim 1, said R_1, R_2 and R_3 are independently selected from the group consisting of a hydrogen atom, a halo, a hydroxy, a C_1-C_6 low alkyl, a C_2-C_6 low alkenyl, a C_1-C_6 low alkoxy, an aryloxy, an amino, a C_1-C_6 alkylamino, a C_1-C_{10} aralkylamino, an arylamino, an acylamino, a saturated heterocyclic, an aryl, a heteroaryl, and a C_1-C_{10} heteroaralkyl group; or neighboring R_2 and R_3 form a ring by binding with each other;

said R_4, R_5, R_6 and and R_7 are independently selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl and an aryl group; or R_4, R_5, R_6 and

and R_7 independently form a ring by binding with a neighboring substitution group;

X is an oxygen or sulfur atom;

Y is an oxygen atom or N-R_8, wherein R_8 is selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl, an aryl, and a C_1-C_{10} aralkyl group;

said aryl group is a phenyl group;

said heteroaryl and saturated heterocyclic groups are selected from furan, thiophene, pyridine, piperidine, piperazine, morpholine, pyrolidine and benzodioxol; and

said aryl and heteroaryl groups are such that 1 to 4 substitution groups selected from the group consisting of a halo, a hydroxy, a C_1-C_6 low alkyl, a C_1-C_6 low alkoxy, an amino, a cyano, a nitro, a carbonyl and a carboxyl group are substituted.

4.(Newly Amended) In claim 1, said compound of formula 1 is selected from the group consisting of

3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

~~**6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-on,**~~

~~**5-vinyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-on,**~~

6,8-dichloro-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6,8-dihydroxy-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-hydroxy-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-1-oxo-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl acetic ester,

8-methoxy-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6,8-dimethyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-furan-2-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-thiophene-2-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-pyridine-2-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-fluorophenyl)-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-chloro-phenyl)-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-morpholine-4-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-(4-methyl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-(4-pyrimidine-2-yl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-fluorophenylamino)-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-chloro-phenylamino)-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-trifluoromethyl-phenylamino)-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-*p*-tolylamino-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-phenylamino-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-phenetylamino-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-[(benzo[1,3]dioxol-5-yl-methyl)-amino]-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-8-phenoxy-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-benzylamino-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-methoxy-benzylamino)-6-methyll-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-amino-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-acetamido-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-benzamido-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-hydroxy-6-methyl-5-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-chloro-6-methyl-5-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-methyl-5-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-hydroxy-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-chloro-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-methyl-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

1-oxo-6-phenyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl acetic ester,

8-methoxy-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-methylamino-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-dimethylamino-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-phenyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-morpholine-4-yl-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-phenyl-8-pyrolidine-1-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-fluorophenylamino)-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-(4-methoxy-benzylamino)-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,,

8-amino-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-acetamido-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-benzamido-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-hydroxy-8-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-chloro-8-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-methyl-6-(thiophene-2-yl)-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-(furan-2-yl)-8-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-(benzo[d][1,3]dioxol-6-yl)-8-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-(4-(dimethylamino)phenyl)-8-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-hydroxy-6-propyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-chloro-6-propyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-propyl-6-chloro-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-morpholine-4-yl-6-propyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

1-oxo-6-propyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl acetic ester

8-(4-methoxy-benzylamino)-6-propyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-amino-6-propyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

N-(1-oxo-6-propyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl)-acetamide,

3,4-dihydro-2-oxa-aza-phenanthrene-1-on,

3,4-dihydro-pyrano[3,4-*c*]pyridine-1-thione,

2-(4-methoxy-benzyl)-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

2-benzyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

3-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

3-phenyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

8-methyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

2,8-dimethyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

2-benzyl-8-methyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

6-cyclohexyl-8-hydroxy-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-cyclohexyl-1-oxo-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl acetic acid methyl ester,

8-chloro-6-cyclohexyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-cyclohexyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-cyclohexyl-8-(4-mthoxy-benzylamino)-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-amino-6-cyclohexyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-hydroxy-6-isopropyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-isopropyl-1-oxo-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl acetic acid methyl ester,

8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-isopropyl-8-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on;

6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

1-oxo-6-thiophene-2-yl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl acetic acid methyl ester,

6-ethyl-8-hydroxy-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-ethyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl acetic acid methyl ester,

8-chloro-6-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-amino-6-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-ethyl-8-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-ethyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-amino-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

2-ethyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-furan-2-yl-6-phenyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-phenyl-8-thiophene-2-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-phenyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-chloro-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-isopropyl-6-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-isopropyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-cyclohexyl-6-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-cyclohexyl-6-morpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-cyclohexyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-propyl-6-pyrrolidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-piperidine-1-yl-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-morpholine-4-yl-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-amino-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-(4-methoxybenzylamino)-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-hydroxy-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-2,6-dimethyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

2-ethyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

6-amino-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-amino-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

4-fluoro-N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide,

4-chloro-N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide,

N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide,

N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-methoxy-benzenesulfonamide,

N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-methyl-benzenesulfonamide,

8-[4-(2-hydroxyethyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-benzylpiperazine-1-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(4-phenylpiperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-[4-(2-ethoxyphenyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-[4-(2-chlorophenyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(4-pyridine-2-yl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(4-methyl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-morpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-pyrrolidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(methylphenethylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-[1,4']bipiperidinyl-1'-yl-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-benzylpiperidinyl-1-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

1-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-3-carboxylamide,

1-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-3-carboxylic acid ethyl ester,

1-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-4-carboxylic acid ethyl ester,

5-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-ylamino)-pentanoic acid,

6-isopropyl-8-thiomorpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-tert-butyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(1,1-dioxo-thiomorpholine-4-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-tert-butyl-8-chloro-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-methoxy-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-chloro-8-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-ethyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-amino-8-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthylidine-2-carboxylic acid methyl ester,

2-(2-dimethylaminoethyl)-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-6-methyl-2-(2-pyrrolidine-1-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-6-methyl-2-(2-morpholine-4-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-2-(2-hydroxyethyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

[8-(4-fluorophenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthylidine-2-yl]-acetic acid ethyl ester,

8-(4-fluorophenyl)-6-methyl-2-pyridine-2-ylmethyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

2-[1,3]dioxolane-2-yl-methyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

2-(2-[1,3]dioxolane-2-yl-ethyl)-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

[8-(4-fluorophenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthylidine-2-yl]-acetic acid,

N-(8-ethyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-fluoro-benzenesulfonamide,

N-(8-ethyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-3-fluoro-benzenesulfonamide;

and

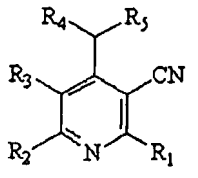
their pharmaceutically acceptable salts.

5. A method for preparing a compound of the following formula 1 comprising:

(a) reacting a compound of the following formula 2 with an alkylester compound containing R_6 in the presence of a base to obtain a compound of the following formula 3;

(b) reacting said compound of the following formula 3 with a reducing agent or a metal reagent containing R_7 at 0 °C or room temperature to obtain an alcohol compound of the following formula 4; and

(c) performing a cyclization of said alcohol compound of the following formula 4 to obtain a compound of the following formula 1,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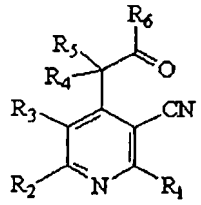
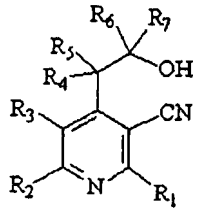
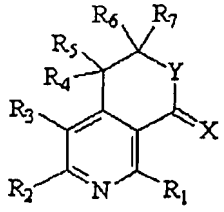

(3)


(4)

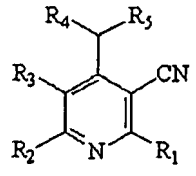

(1)

wherein R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are the same as defined in claim 1, and X and Y individually represent an oxygen atom.

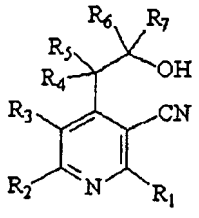
6. A method for preparing a compound of the following formula 1 comprising:

(a) reacting a compound of the following formula 2 with an alkylcarbonyl compound represented by R_6COR_7 in the presence of a base to obtain a compound of the following formula 4; and

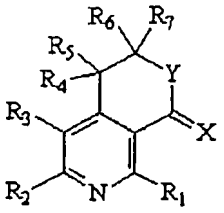
(b) performing a cyclization of said alcohol compound of the following formula 4 to obtain a compound of the following formula 1,



(2)



(4)



(1)

wherein R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are the same as defined in claim 1, and X and Y individually represent an oxygen atom.

7. In claim 5, said alkylester compound containing R_6 is represented by R_6COOCH_3.

8. In claim 5, said metal reagent containing R_7 is a Grignard reagent of R_7M, wherein M is an alkali metal, or $R_{7\ mg}X^1$, wherein X is a halogen atom).

9. In claim 5 or claim 6, said base is selected from the group consisting of lithium

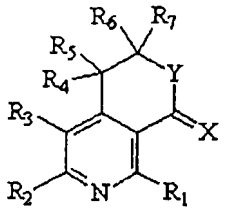
bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium diisopropylamide, sodium hydride, potassium hydride and lithium hydride.

10. In claim 5 or claim 6, said cyclization is performed by using a strong acid reagent of conc. HCl.

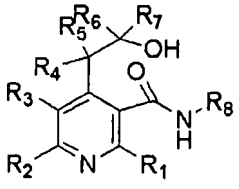
11. A method for preparing a compound of the following formula 1 comprising:

(a) reacting a compound of the following formula 1, wherein X and Y are individually an oxygen atom, with an amine compound represented by R_8NH_2 to obtain a compound of the following formula 8; and

(b) performing a cyclization of said compound of the following formula 8 to obtain a compound of the following formula 1, wherein X is an oxygen atom and Y is N-R_8,



(1)



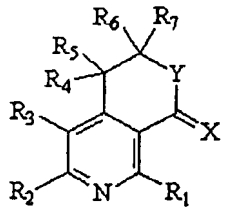
(8)

wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, X and Y are the same as defined in claim 1.

12. In claim 11, said cyclization is performed by using diethyl azodicarboxylate and

triphenylphosphine.

13.(Newly Amended) A pharmaceutical composition having an inhibitory effect on the production of cytokines wherein said composition comprises a compound of the following formula 1 or its pharmaceutically acceptable salt,



(1)

~~wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X and Y are the same as defined in claim 1.~~

wherein R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from the group consisting of a hydrogen atom, a halo, a cyano, a nitro, an acyl, a hydroxy, an amino, a C_1-C_6 low alkyl, a C_2-C_6 low alkenyl, a C_1-C_6 low alkoxy, a C_1-C_6 alkylthio, a C_1-C_{10} alkylamino, a C_4-C_9 cycloalkylamino, a C_4-C_9 heterocycloalkylamino, a C_1-C_{10} aralkylamino, an arylamino, an acylamino, a saturated heterocyclic, an acyloxy, a C_1-C_6 alkylsulfinyl, a C_1-C_6 alkylsulfonyl, a C_1-C_6 alkylsulfonylamino, an arylsulfinyl, an arylsulfonyl, an arylsulfonylamino, an aryl, a heteroaryl, a C_1-C_{10} aralkyl, a C_1-C_{10} heteroaralkyl, an aryloxy and a heteroaryloxy group; or R_1, R_2, R_3, R_4, R_5, R_6 and R_7 independently form a ring by binding with a neighboring substitution group;

X is an oxygen or sulfur atom;

Y is an oxygen atom or N-R_8, wherein R_8 is selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl, an acyl, an aryl, a heteroaryl, a C_1-C_{10} aralkyl and a C_1-C_{10} heteroaralkyl group; or forms a ring by binding with a

neighboring substitution group of R_6 or R_7;

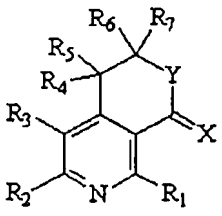
said aryl group is selected from a phenyl, a naphthyl and a fused phenyl group;

said heteroaryl and saturated heterocyclic groups are a heterocyclic ring with a pentagonal or hexagonal shape having 1 to 3 heteroatoms selected from an oxygen, a nitrogen, and a sulfur atom; or a fused heterocyclic ring; and

said aryl and heteroaryl groups are such that 1 to 4 substitution groups selected from the group consisting of a halo, a hydroxy, a C_1-C_6 low alkyl, a C_1-C_6 low alkoxy, an amino, a cyano, a nitro, a carbonyl and a carboxyl group are substituted.

14. In claim 13, said cytokine is TNF-α.

15.(Newly Amended) A therapeutic agent comprising a compound of the following formula 1 or its pharmaceutically acceptable salt effective in treating inflammatory diseases,



(1)

~~wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X and Y are the same as defined in claim 1.~~

wherein R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from the group consisting of a hydrogen atom, a halo, a cyano, a nitro, an acyl, a hydroxy, an amino, a C_1-C_6 low alkyl, a C_2-C_6 low alkenyl, a C_1-C_6 low alkoxy, a C_1-C_6

alkylthio, a C_1-C_{10} alkylamino, a C_4-C_9 cycloalkylamino, a C_4-C_9 heterocycloalkylamino, a C_1-C_{10} aralkylamino, an arylamino, an acylamino, a saturated heterocyclic, an acyloxy, a C_1-C_6 alkylsulfinyl, a C_1-C_6 alkylsulfonyl, a C_1-C_6 alkylsulfonylamino, an arylsulfinyl, an arylsulfonyl, an arylsulfonylamino, an aryl, a heteroaryl, a C_1-C_{10} aralkyl, a C_1-C_{10} heteroaralkyl, an aryloxy and a heteroaryloxy group; or R_1, R_2, R_3, R_4, R_5, R_6 and R_7 independently form a ring by binding with a neighboring substitution group;

X is an oxygen or sulfur atom;

Y is an oxygen atom or N-R_8, wherein R_8 is selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl, an acyl, an aryl, a heteroaryl, a C_1-C_{10} aralkyl and a C_1-C_{10} heteroaralkyl group; or forms a ring by binding with a neighboring substitution group of R_6 or R_7;

said aryl group is selected from a phenyl, a naphthyl and a fused phenyl group;

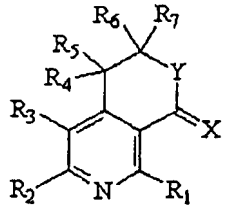
said heteroaryl and saturated heterocyclic groups are a heterocyclic ring with a pentagonal or hexagonal shape having 1 to 3 heteroatoms selected from an oxygen, a nitrogen, and a sulfur atom; or a fused heterocyclic ring; and

said aryl and heteroaryl groups are such that 1 to 4 substitution groups selected from the group consisting of a halo, a hydroxy, a C_1-C_6 low alkyl, a C_1-C_6 low alkoxy, an amino, a cyano, a nitro, a carbonyl and a carboxyl group are substituted.

16. In claim 15, said inflammatory diseases are selected from the group consisting of rheumatic arthritis, multiple sclerosis, Crohn' disease, ulcerative colitis, graft-versus-

host disease, systnemic erythematosus lupus, toxic shock syndrome, osteoarthritis and insulin-dependent diabetes.

17.(Newly Amended) A therapeutic agent having an anti-inflammatory and analgesic effect comprising a compound of the following formula 1 or its pharmaceutically acceptable salt,



(1)

~~wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X and Y are the same as defined in claim 1.~~

wherein R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from the group consisting of a hydrogen atom, a halo, a cyano, a nitro, an acyl, a hydroxy, an amino, a C_1-C_6 low alkyl, a C_2-C_6 low alkenyl, a C_1-C_6 low alkoxy, a C_1-C_6 alkylthio, a C_1-C_{10} alkylamino, a C_4-C_9 cycloalkylamino, a C_4-C_9 heterocycloalkylamino, a C_1-C_{10} aralkylamino, an arylamino, an acylamino, a saturated heterocyclic, an acyloxy, a C_1-C_6 alkylsulfinyl, a C_1-C_6 alkylsulfonyl, a C_1-C_6 alkylsulfonylamino, an arylsulfinyl, an arylsulfonyl, an arylsulfonylamino, an aryl, a heteroaryl, a C_1-C_{10} aralkyl, a C_1-C_{10} heteroaralkyl, an aryloxy and a heteroaryloxy group; or R_1, R_2, R_3, R_4, R_5, R_6 and R_7 independently form a ring by binding with a neighboring substitution group;

X is an oxygen or sulfur atom;

Y is an oxygen atom or N-R_8, wherein R_8 is selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl, an acyl, an aryl, a heteroaryl, a

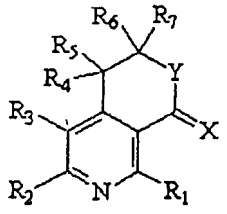
C_1-C_{10} aralkyl and a C_1-C_{10} heteroaralkyl group; or forms a ring by binding with a neighboring substitution group of R_6 or R_7;

said aryl group is selected from a phenyl, a naphthyl and a fused phenyl group;

said heteroaryl and saturated heterocyclic groups are a heterocyclic ring with a pentagonal or hexagonal shape having 1 to 3 heteroatoms selected from an oxygen, a nitrogen, and a sulfur atom; or a fused heterocyclic ring; and

said aryl and heteroaryl groups are such that 1 to 4 substitution groups selected from the group consisting of a halo, a hydroxy, a C_1-C_6 low alkyl, a C_1-C_6 low alkoxy, an amino, a cyano, a nitro, a carbonyl and a carboxyl group are substituted.

18.(Newly Amended) A therapeutic agent for treating immune-related diseases comprising a compound of the following formula 1 or its pharmaceutically acceptable salt,



(1)

~~wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X and Y are the same as defined in claim 1.~~

wherein R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from the group consisting of a hydrogen atom, a halo, a cyano, a nitro, an acyl, a hydroxy, an amino, a C_1-C_6 low alkyl, a C_2-C_6 low alkenyl, a C_1-C_6 low alkoxy, a C_1-C_6 alkylthio, a C_1-C_{10} alkylamino, a C_4-C_9 cycloalkylamino, a C_4-C_9

heterocycloalkylamino, a C_1-C_{10} aralkylamino, an arylamino, an acylamino, a saturated heterocyclic, an acyloxy, a C_1-C_6 alkylsulfinyl, a C_1-C_6 alkylsulfonyl, a C_1-C_6 alkylsulfonylamino, an arylsulfinyl, an arylsulfonyl, an arylsulfonylamino, an aryl, a heteroaryl, a C_1-C_{10} aralkyl, a C_1-C_{10} heteroaralkyl, an aryloxy and a heteroaryloxy group; or R_1, R_2, R_3, R_4, R_5, R_6 and R_7 independently form a ring by binding with a neighboring substitution group;

X is an oxygen or sulfur atom;

Y is an oxygen atom or N-R_8, wherein R_8 is selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl, an acyl, an aryl, a heteroaryl, a C_1-C_{10} aralkyl and a C_1-C_{10} heteroaralkyl group; or forms a ring by binding with a neighboring substitution group of R_6 or R_7;

said aryl group is selected from a phenyl, a naphthyl and a fused phenyl group;

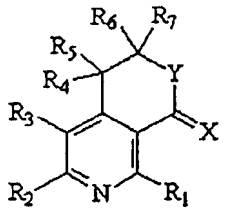
said heteroaryl and saturated heterocyclic groups are a heterocyclic ring with a pentagonal or hexagonal shape having 1 to 3 heteroatoms selected from an oxygen, a nitrogen, and a sulfur atom; or a fused heterocyclic ring; and

said aryl and heteroaryl groups are such that 1 to 4 substitution groups selected from the group consisting of a halo, a hydroxy, a C_1-C_6 low alkyl, a C_1-C_6 low alkoxy, an amino, a cyano, a nitro, a carbonyl and a carboxyl group are substituted.

19. In claim 18, said immune-related diseases are selected from the group consisting of glomerulonephritis, dermatitis, asthma, stroke, cardiac infarction, acute respiratory distress syndrome, postinjury multiple organ failure, purulent meningitis, necrotizing

enterocolitis, parahemodialysis syndrome, septic shock, and post-menopausal osteoporosis.

20.(Newly Amended) A therapeutic agent for treating chronic inflammatory diseases comprising a compound of the following formula 1 or its pharmaceutically acceptable salt,



(1)

~~wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, X and Y are the same as defined in claim 1.~~

wherein R_1, R_2, R_3, R_4, R_5, R_6 and R_7 are independently selected from the group consisting of a hydrogen atom, a halo, a cyano, a nitro, an acyl, a hydroxy, an amino, a C_1-C_6 low alkyl, a C_2-C_6 low alkenyl, a C_1-C_6 low alkoxy, a C_1-C_6 alkylthio, a C_1-C_{10} alkylamino, a C_4-C_9 cycloalkylamino, a C_4-C_9 heterocycloalkylamino, a C_1-C_{10} aralkylamino, an arylamino, an acylamino, a saturated heterocyclic, an acyloxy, a C_1-C_6 alkylsulfinyl, a C_1-C_6 alkylsulfonyl, a C_1-C_6 alkylsulfonylamino, an arylsulfinyl, an arylsulfonyl, an arylsulfonylamino, an aryl, a heteroaryl, a C_1-C_{10} aralkyl, a C_1-C_{10} heteroaralkyl, an aryloxy and a heteroaryloxy group; or R_1, R_2, R_3, R_4, R_5, R_6 and R_7 independently form a ring by binding with a neighboring substitution group;

X is an oxygen or sulfur atom;

Y is an oxygen atom or N-R_8, wherein R_8 is selected from the group consisting of a hydrogen atom, a C_1-C_6 low alkyl, an acyl, an aryl, a heteroaryl, a

C_1-C_{10} aralkyl and a C_1-C_{10} heteroaralkyl group; or forms a ring by binding with a neighboring substitution group of R_6 or R_7;

said aryl group is selected from a phenyl, a naphthyl and a fused phenyl group;

said heteroaryl and saturated heterocyclic groups are a heterocyclic ring with a pentagonal or hexagonal shape having 1 to 3 heteroatoms selected from an oxygen, a nitrogen, and a sulfur atom; or a fused heterocyclic ring; and

said aryl and heteroaryl groups are such that 1 to 4 substitution groups selected from the group consisting of a halo, a hydroxy, a C_1-C_6 low alkyl, a C_1-C_6 low alkoxy, an amino, a cyano, a nitro, a carbonyl and a carboxyl group are substituted.

21.(Amended) In claim 20, said chronic inflammatory diseases are psoriatic arthritis, psoriatis, ankylosing spondylitis, adult-onset Still's disease, polymyositis, dermatomyositis, arteriosclerosis or vasculitis such as Behcet disease and Wegener's granulomatosis.

with a biomembrane receptor thereby triggering a series of signal transduction chain reaction; 2)the terminal stage of controlling expression of a gene encoding an inflammation-related protein by means of transcription factors within a nucleus; and 3) an intermediate stage which consists of a series of signal transduction chain reactions that link between the intial stage and the terminal stage.

Examples of well-known inflammation signal factor at the initial stage are tumor necrosis factor (TNF; also referred to as TNF-α) and interleukin-1 (IL-1). Examples of well-known inflammation signal factor at the terminal stage are activating protein-1 (AP-1; activating protein-1), nuclear transcription factor kappa B (NFkB) and nuclear factor of activated T cells (NFAT). The chain reactions at the intermediate stage are not well identified but it appears that lipocortin, cyclooxygenase-1, 2, and PLA_2 are involved in this stage.

Referring to inflammation-causing factors, TNF-α, produced mainly in activated macrophage and T cells, is the most powerful inflammatory cytokine and stimulates the production of other inflammatory cytokines such as IL-1, IL-6 and IL-8 as well as transcription factors such as NK-kB and c-jun/Ap-1. In fact, TNF-α is related with the development of inflammatory diseases or immune-related diseases such as toxic shock syndrome, insulin-dependent diabetes, multiple sclerosis, rheumatic arthritis, osteoarthritis, Crohn's disease and ulcerative colitis. In particular, TNF-α is also related with chronic inflammatory diseases such as psoriatic arthritis, psoriatis, ankylosing spondylitis, adult-onset Still's disease, polymyositis, dermatomyositis, arteriosclerosis, and vasculitis such as Behcet disease and Wegener's granulomatosis Behcet disease and Wegener's granulomatosis. IL-1 is also a powerful inflammatory cytokine comparable to TNF-α and increases the

expression

8-methyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

2,8-dimethyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

2-benzyl-8-methyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthyridine-1-on,

6-cyclohexyl-8-hydroxy-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-cyclohexyl-1-oxo-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl acetic acid methyl ester,

8-chloro-6-cyclohexyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-cyclohexyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-cyclohexyl-8-(4-mthoxy-benzylamino)-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-amino-6-cyclohexyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

8-hydroxy-6-isopropyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-isopropyl-1-oxo-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-8-yl acetic acid methyl ester,

8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-isopropyl-8-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-on,

6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

1-oxo-6-thiophene-2-yl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl acetic acid methyl ester,

6-ethyl-8-hydroxy-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-ethyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl acetic acid methyl ester,

8-chloro-6-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-amino-6-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-ethyl-8-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-ethyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-amino-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

2-ethyl-8-methyl-6-phenyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-furan-2-yl-6-phenyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-phenyl-8-thiophene-2-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-phenyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-chloro-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-isopropyl-6-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-isopropyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-cyclohexyl-6-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-cyclohexyl-6-morpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-cyclohexyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-propyl-6-pyrrolidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-piperidine-1-yl-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-morpholine-4-yl-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-amino-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-(4-methoxybenzylamino)-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-hydroxy-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-2,6-dimethyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

2-ethyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

6-amino-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-amino-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

4-fluoro-N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide,

4-chloro-N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide,

N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide,

N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-methoxy-benzenesulfonamide,

N-(8-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-methyl-benzenesulfonamide,

8-[4-(2-hydroxyethyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-benzylpiperazine-1-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(4-phenylpiperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-[4-(2-ethoxyphenyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-[4-(2-chlorophenyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(4-pyridine-2-yl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(4-methyl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-morpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-pyrrolidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-isopropyl-8-(methylphenethylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-[1,4']bipiperidinyl-1'-yl-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-benzylpiperidinyl-1-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

1-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-3-acrboxylic acid amide,

1-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-3-acrboxylic acid ethyl ester,

1-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-4-acrboxylic acid ethyl ester,

5-(6-isopropyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-ylamino)-pentanoic acid,

6-isopropyl-8-thiomorpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-*tert*-butyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(1,1-dioxo-thiomorpholine-4-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-*tert*-butyl-8-chloro-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-methoxy-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-chloro-8-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-ethyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

6-amino-8-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one,

8-(4-fluorophenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthylidine-2-acrboxylic acid methyl ester,

2-(2-dimethylaminoethyl)-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-6-methyl-2-(2-pyrrolidine-1-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-6-methyl-2-(2-morpholine-4-yl-ethyl)-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

8-(4-fluorophenyl)-2-(2-hydroxyethyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

[8-(4-fluorophenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthylidine-2-yl]-acetic acid ethyl ester,

8-(4-fluorophenyl)-6-methyl-2-pyridine-2-yl-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

2-[1,3]dioxolane-2-yl-methyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

2-(2-[1,3]dioxolane-2-yl-ethyl)-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2H-[2,7]naphthylidine-1-one,

[8-(4-fluorophenyl)-6-methyl-1-oxo-3,4-dihydro-1H-[2,7]naphthylidine-2-yl]-acetic acid,

N-(8-ethyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-fluoro-benzenesulfonamide,

N-(8-ethyl-1-oxo-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-3-fluoro-benzenesulfonamide; and

their pharmaceutically acceptable salts.

In another preferred embodiment, the present invention provides a method for preparing pyridine derivatives of the above formula 1.

Of the pyridine derivatives of the present invention, those of the above formula 1, wherein X and Y are individually an oxygen atom, can be prepared by 3 different methods according to the following reaction schemes 1, 2 and 3.

pharmaceutical composition comprising the compound of the above formula 1 or its pharmaceutically acceptable salts for the treatment and prevention of diseases.

That is, the present invention comprises a compound of the above formula 1 or its pharmaceutically acceptable salts to be useful as a therapeutic agent for treating inflammatory diseases, immune diseases, chronic inflammatory diseases and an anti-inflammatory and analgesic agent, and a medical use of a pharmaceutical composition containing the same.

The pharmaceutical composition of the present invention is effective in treating diseases caused by TNF-α, IL-1α, IL-1β and IFN-γ. More specifically, it is effective in treating diseases such as (i) inflammatory diseases or immune diseases such as rheumatic arthritis, multiple sclerosis, Crohn's disease, infectious intestinal diseases such as ulcerative colitis, graft-versus-host disease, systemic erythematosus lupus, toxic shock syndrome, osteoarthritis and insulin-dependent diabetes; (ii) chronic inflammatory diseases such as psoriatic arthritis, psoriatis, ankylosing spondylitis, adult-onset Still's disease, polymyositis, dermatomyositis, vasculitis such as Behcet disease and Wegener's granulomatosis; and is also effective as (iii) an anti-inflammatory and analgesic agent. In addition, it is effective in treating diseases such as glomerulonephritis, dermatitis, asthma, stroke, cardiac infarction, acute respiratory distress syndrome, postinjury multiple organ failure, purulent meningitis, necrotizing enterocolitis, parahemodialysis syndrome, septic shock, and post-menopausal osteoporosis.

Examples

A better understanding of the present invention may be obtained in light of the

1.32(d, *J*=6.6Hz, 6H).

Example 144: Synthesis of 6-isopropyl-8-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-on

481 mg (95%) of 6-isopropyl-8-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-on was obtained in white solid using the method same as in Example 32 except that 350 mg of 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-on and 4-methoxy-benzylami were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-on and piperidine.

^{1}H NMR(300 MHz, $CDCl_3$) δ 8.48(br s, 1H), 7.29-7.33(m, 2H), 6.83-6.87(m, 2H), 6.23(s, 1H), 4.71(d, *J*=6.0Hz, 2H), 4.44(t, *J*=6.3Hz, 2H), 3.79(s, 3H), 2.84-2.86(m, 3H), 1.24(d, *J*=6.0Hz, 6H).

not claimed in claim 1

Example 145: Synthesis of 2-ethyl-8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one

467 mg (93%) of 2-ethyl-8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one was obtained in light yellow solid using the same method as in Example 122 except that 450 mg (1.905 mmol) of 8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one and 0.17 ml (2.286 mmol) of bromoethane were used instead of 2*H*-[2,7]naphthylidine-1-one and benzyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39(t, 3H, *J*=7.2Hz), 3.20(s, 3H), 4.03(q, 2H, *J*=7.2Hz), 6.43(d, 1H, *J*=7.2Hz), 7.24(d, 1H, *J*=7.2Hz), 7.41-7.52(m, 3H), 7.56(s, 1H), 8.08-8.12(m, 2 H).

Example 146: Synthesis of 2-ethyl-8-methyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

226 mg (86%) of 2-ethyl-8-methyl-6-phenyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 124 except that 260 mg (0.984 mmol) of 2-ethyl-8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one was used instead of 8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24(t, 3H, *J*=7.2Hz), 2.96-3.00(m, 5H), 3.55(t, 2H, *J* =6.3Hz), 3.63(q, 2H, *J* =7.2Hz), 7.38(s, 1H), 7.39-7.50(m, 3H), 8.01 -8.05(m, 2 H)

Example 147: Synthesis of 8-furan-2-yl-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one

328 mg (98%) of 6-phenyl-8-furan-2-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one was obtained in light yellow solid using the same method as in Example 27 except that 8-chloro-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one (300 mg, 1.155 mmol) was used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one .

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11(t, 2H, *J*=5.7Hz), 4.58(t, 2H, *J* =5.7Hz), 6.57-6.58(m, 1H), 7.24-7.25(m, 1H), 7.45-7.54(m, 4H), 7.60-7.61(m, 1H), 8.08-8.13 (m, 2H)

Example 148: Synthesis of 6-phenyl-8-thiophene-2-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one

334 mg (94%) of 6-phenyl-8-thiophene-2-yl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one was obtained in white solid using the same method as in Example 27 except that 8-chloro-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one (300 mg, 1.155 mmol) and 2-(tributylstannyl)thiophene (734 mg, 2.310 mmol) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one and 2-(tributylstannyl)furan.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11(t, 2H, *J*=5.7Hz), 4.57 (t, 2H, *J*=5.7Hz), 7.09-7.12(m, 1H), 7.48-7.55(m, 5H), 7.87-7.88(m, 1H), 8.12-8.16 (m, 2H)

Example 149: Synthesis of 8-(4-fluorophenyl)-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one

186 mg (38%) of 8-(4-fluorophenyl)-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one was obtained in white solid using the same method as in Example 30 except that 8-chloro-6-phenyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one (400 mg, 1.540 mmol) was used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one .

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15(t, 2H, *J*=5.7Hz), 4.62(t, 2H, *J* =5.7Hz), 7.10-7.18(m, 2H), 7.47-7.54(m, 3H), 7.60(s, 1H), 7.64-7.71(m, 2H), 8.09-8.14 (m, 2H)

Example 150: Synthesis of 8-(4-fluorophenyl)-6-isopropyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one

275 mg (44%) of 8-(4-fluorophenyl)-6-isopropyl -3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one was obtained in white solid using the same method as in Example 30 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one (500 mg,

2.216 mmol) was used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-*c*]pyridine-1-one .

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34(d, 6H, *J*=7.2Hz), 3.06(t, 2H, *J* =5.7Hz), 3.09-3.19(m, 1H), 4.56(t, 2H, *J* =5.7Hz), 7.04(s, 1H), 7.08-7.13(m, 2H), 7.55 -7.60(m, 2H)

Example 151: Synthesis of 2-(4-fluorophenyl)-4,6-dimethyl-nicotinonitrile

2-chloro-4,6-dimethyl-nicotinonitrile (15.0 g, 90.031 mmol), 4-fluorophenylboric acid (15.1 g, 108.037 mmol) and anhydrous potassium carbonate (24.9 g, 180.062 mmol) were suspended in a mixture of anhydrous toluene (300 ml) and anhydrous ethanol (15 ml). After 1 hr of stirring at room temperature under nitrogen atmosphere, $Pd(PPh_3)_4$ (5.2 g, 4.502 mmol) was added and heat reflux was performed for 20 hours at 110 °C under nitrogen atmosphere . The reaction solution was concentrated under reduced pressure. After adding a saturated aqueous ammonium chloride solution (200 ml), distilled water (200 ml) was added and the solution was extracted with methylene chloride (400 ml × 2). The organic layer was dried with anhydrous sodium sulfate, filtered and concentrated. A silica gel column chromatography (20% EtOAc/hexane) was performed on the resulting residue to obtain 20.05 g (98 %) of white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58(s, 3H), 2.63(s, 3H), 7.11(s, 1H), 7.15-7.22(m, 2H), 7.85-7.90(m, 2H)

Example 152: Synthesis of 4-(2-dimethylamino-vinyl)-2-(4-fluorophenyl)-6-methyl-nicotinonitrile

2-(4-Fluorophenyl)-4,6-dimethyl-nicotinonitrile (20.0 g, 88.398 mmol) was dissolved in anhydrous DMF (180 ml). N,N-dimethylformamide dimethylacetal (94%, 37.6 ml, 265.193 mmol) was added and the mixture was stirred for 15 hours at 120 °C under nitrogen atmosphere. The reaction solution was concentrated under reduced pressure, dryied in vacuum and recrystallized with EtOAc/hexane. After keeping for 15 hours in a refrigerator, the resulting solution was filtered under reduced pressure and dired in vacuum to obtain 20.52 g (83%) of yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52(s, 3H), 3.01(s, 6H), 5.38(d, 1H, *J*=13.5Hz), 7.01(s, 1H), 7.11-7.19(m, 2H), 7.30(d, 1H, *J*=13.5Hz), 7.76-7.83(m, 2H)

Example 153: Synthesis of 8-(4-fluorophenyl)-6-methyl-2*H*-[2,7]naphthylidine-1-one

4-(2-dimethylamino-vinyl)-2-(4-fluorophenyl)-6-methyl-nicotinonitrile (18.5 g, 65.759 mmol) was dissolved in acetic acid (50 ml). Sulfuric acid (50 ml) was added while stirring the solution at 0 °C. Then, heat reflux was peroformed for 6 hours at 110 °C. The reaction solution was cooled to room temperature and poured to ice water (800 g). The solution was neutralized by slowly adding a 20% sodium hydroxide aqueous solution, while stirring at 0 °C. The precipitated solid was filtered under reduced pressure, washed several times with distilled water and dired in vacuum for15 hours at 45 °Cto obtain 14.44 g (86%) of yellow solid.

^{1}H NMR (300 MHz, DMSO-d 6) δ 2.54(s, 3H), 6.48(d, 1H, *J*=7.2Hz), 7.11-7.19(m, 2H), 7.36(d, 1H, *J*=7.2Hz), 7.39-7.46(m, 3H)

Example 154: Synthesis of 8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

195 mg (88%) of 8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 124 except that 8-(4-fluorophenyl)-6-methyl-2*H*-[2,7]naphthylidine-1-one (220 mg, 0.865 mmol) was used instead of 8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2. 60(s, 3H), 2.96(t, 2H, *J* =6.3Hz), 3.53-3.58(m, 2H) 6.05(brs, 1H), 7.01(s, 1H), 7.04-7.12(m, 2H), 7.47-7.54(m, 2H)

Example 155: Synthesis of 8-(4-fluorophenyl)-2,6-dimethyl-2*H*-[2,7]naphthylidine-1-one

368 mg (87%) of 8-(4-fluorophenyl)-2,6-dimethyl-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 122 except that 8-(4-fluorophenyl)-6-methyl-2*H*-[2,7]naphthylidine-1-one (400 mg, 1.573 mmol) and iodomethane (0.12 ml, 1.888 mmol) were used instead of 2*H*-[2,7]naphthylidine-1-oneand benzyl chloride .

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.66(s, 3H), 3.47(s, 3H), 6.39(d, 1H, *J*=7.5Hz), 7.08 -7.16(m, 2H), 7.18(s, 1H), 7.25(d, 1H, *J*=7.5Hz), 7.40 -7.46(m, 2H)

Example 156: Synthesis of 8-(4-fluorophenyl)-2,6-dimethyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

146 mg (73%) of 8-(4-fluorophenyl)-2,6-dimethyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in

Example 124 except that 8-(4-fluorophenyl)-2,6- dimethyl-2*H*-[2,7]naphthylidine-1-one (200 mg, 0. 745 mmol) was used instead of 8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58(s, 3H), 2.96(t, 2H, *J*=6.3Hz), 3.09(s, 3H), 3.62(t, 2 H, *J*=6.3Hz), 6.97(s, 1H), 7.03-7.11(m, 2H), 7.40 -7.46(m, 2H)

Example 157: Synthesis of 2-ethyl-8-(4-fluorophenyl)-6-methyl-2*H*-[2,7]naphthylidine-1-one

394 mg (93%) of 2-ethyl-8-(4-fluorophenyl)-6-methyl-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 122 except that 8-(4-fluorophenyl)-6-methyl-2*H*-[2,7]naphthylidine-1-one (380 mg, 1.495 mmol) and bromoethane (0.13 ml, 1.794 mmol) were used instead of 2*H*-[2,7]naphthylidine-1-one and benzyl chloride .

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29(t, 3H, *J*=7.2Hz), 2.66(s, 3H), 3.94(q, 2H, *J*=7.2Hz), 6.40(d, 1H, *J* =7.2Hz), 7.07-7.15(m, 2H), 7.17(s, 1H), 7.25(d, 1H, *J*=7.2Hz), 7.41-7.48(m, 2H)

Example 158: Synthesis of 2-ethyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

149 mg (67%) of 2-ethyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 124 except that 2-ethyl-8-(4-fluorophenyl)-6-methyl-2*H*-[2,7]naphthylidine-1-one (220 mg, 0.779 mmol) was used instead of 8-methyl-6-phenyl-2*H*-[2,7]naphthylidine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17(t, 3H, *J*=7.2Hz), 2.58(s, 3H), 2.94(t, 2H, *J*=6.3Hz), 3.54(q, 2H, *J* =7.2Hz), 3.60(t, 2H, *J*=6.3Hz), 6.96(s, 1H), 7.03-7.11(m, 2H), 7.41-7.48(m, 2H)

Example 159: Synthesis of 2-(2-dimethylamino-ethyl)-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one (200 mg, 0.780 mmol) and 2-(dimethylamino)ethyl chloride hydrochloride (225 mg, 1.561 mmol) were dissolved in anhydrous DMF. Triethylamine (0.22 ml, 1.561 mmol) and NaH (60% dispersion in mineral oil, 124 mg, 3.122 mmol) were added while stirring the solution at 0 °C under nitrogen atmosphere. Then, the mixture was stirred at room temperature for 20 hours under nitrogen atmosphere. A saturated ammonium chloride aqueous solution (10 ml) and distilled water (10 ml) were added while stirring the reaction solution at 0 °C. Extraction was performed with 5% MeOH/$CHCl_3$ (40 ml × 2). The organic layer was dried with anhydrous sodium sulfate, filtered and concentrated. A silica gel column chromatography (10 % MeOH/MC) was performed on the resulting residue to obtain 210 mg (82 %) of white solid .

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 6H), 2.49(t, 2H, *J* =6.6Hz), 2.58(s, 3H), 2.94(t, 2H, *J* =6.3Hz), 3.59-3.67(m, 4H), 6.96(s, 1H), 7.04 -7.10(m, 2H), 7.45-7.50(m, 2H)

Example 160: Synthesis of 8-(4-fluorophenyl)-6-methyl-2-(2-pyrrolidine-1-yl-ethyl)-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

200 mg (73%) of 8-(4-fluorophenyl)-6-methyl-2-(2-pyrrolidine-1-yl-ethyl)-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in light yellow solid using the same method as in Example 159 except that 1-(2-chloroethyl)pyrrolidine hydrochloride (265 mg, 1.561 mmol) was used instead of 2-(dimethylamino)ethyl chloride hydrochloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83(brs, 4H), 2.58(s, 3H), 2.67(brs, 4H), 2.77(t, 2H, *J*=6.6Hz), 2.95(t, 2H, *J*=6.3Hz), 3.67-3.73(m, 4H), 6.97(s, 1H), 7.04-7.10(m, 2H), 7.44-7.49(m, 2H)

Example 161: Synthesis of 8-(4-fluorophenyl)-6-methyl-2-(2-morpholine-4-yl-ethyl)-3,4-dihydro -2*H*-[2,7]naphthylidine-1-one

150 mg (52%) of 8-(4-fluorophenyl)-6-methyl-2-(2-morpholine-4-yl-ethyl)-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 159 except that 4-(2-chloroethyl)morpholine hydrochloride (290 mg, 1.561 mmol) was used instead of 2-(dimethylamino)ethyl chloride hydrochloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48(br t, 4H), 2.56(t, 2H, *J*=6.3Hz), 2.59(s, 3H), 2.96(t, 2H, *J*=6.3Hz), 3.61-3.70(m, 8 H), 6.97(s, 1H), 7.04-7.10(m, 2H), 7.43-7.48(m, 2H)

Example 162: Synthesis of 8-(4-fluorophenyl)-6-methyl-2-pyridine-2-yl-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

239 mg (88%) of 8-(4-fluorophenyl)-6-methyl-2-pyridine-2-yl-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same

method as in Example 159 except that 2-picolyl chloride hydrochloride (256 mg, 1.561 mmol) instead of 2-(dimethylamino)ethyl chloride hydrochloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59(s, 3H), 2.92(t, 2H, *J*=6.3Hz), 3.76(t, 2H, *J*=6.3Hz), 4.82(s, 2H), 6.96(s, 1H), 7.0 3-7.11(m, 2H), 7.17-7.21(m, 1H), 7.33(d, 1H, *J*=7.8Hz), 7.45-7.52(m, 2H) , 7.60-7.66(m, 1H), 8.52-8.54(m, 1H)

Example 163: Synthesis of 8-(4-fluorophenyl)-2-(2-hydroxyethyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one

8-(4-Fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one (200 mg, 0.780 mmol) was dissolved in anhydrous DMF and NaH (60% dispersion in mineral oil, 37 mg, 0.936 mmol) was added under nitrogen atmosphere while stirring the solution at 0 °C. After stirring for 30 minutes at room temperature under nitrogen atmosphere, 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (0.14 ml, 0.936 mmol) was added dropwisely at 0 °C . The mixture was stirred for 2 hours at room temperature. A saturated ammonium chloride aqueous solution (10 ml) and distilled water (10 ml) were added while stirring the reaction solution at 0 °C. Then, extraction was performed with EtOAc (50 ml). The organic layer was washed with a saturated sodium chloride aqueous solution, dried with anhydrous sodium sulfate, filtered and concentrated. The resulting residue was dissolved in methanol (10 ml). PTSA (75 mg, 0.390 mmol) was added and the solutionwas stirred for 20 hours at room temperature. The reaction solution was concentrated under reduced pressure and a saturated sodium bicarbonate aqueous solution (10 ml) was added. Then, extraction was performed with 10% MeOH/$CHCl_3$ (20 ml × 2). The organic layer was dried wtih anhydrous sodium sulfate, filtered and

concentrated. A silica gel column chromatography (3 % MeOH/MC) was performed on the resulting residue to obtain 162 mg (69 %) of white solid.

^{1}H NMR (300 MHz, DMSO-d6) δ 2.48(s, 3H), 2.92(t, 2H, *J*=6.3Hz) , 3.44-3.52(m, 4H), 3.64(t, 2H, *J*=6.3Hz), 4.76(brt, 1H, *J*=5.1Hz), 7.11-7.18(m, 3H), 7.41-7.47(m, 2H).

Example 164: Synthesis of [8-(4-fluorophenyl)-6-methyl-1-oxoethyl-3,4-dihydro-1*H*-[2,7]naphthylidine-2-yl]-acetic acid ethyl ester

347 mg (93%) of [8-(4-fluorophenyl)-6-methyl-1-oxoethyl-3,4-dihydro-1*H*-[2,7]naphthylidine-2-yl]-acetic acid ethyl ester was obtained in white solid using the same method as in Example 122 except that 8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one (280 mg, 1.093 mmol) and ethyl bromoacetate (0.15 ml, 1.312 mmol) were used instead of 2*H*-[2,7]naphthylidine-1-oneand benzyl chloride .

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27(t, 3H, *J*=7.2Hz), 2.60(s, 3H), 3.05(t, 2H, *J*=6.3Hz), 3.69(t, 2H, *J*=6.3Hz), 4.19(q, 2H, *J*=7.2Hz), 4.27(s, 2H), 6.99(s, 1H), 7.03-7.10(m, 2H), 7.44-7.51(m, 2H).

Example 165: Synthesis of [8-(4-fluorophenyl)-6-methyl-1-oxoethyl-3,4-dihydro-1*H*-[2,7]naphthylidine -2-yl]-acetic acid

[8-(4-Fluoro-phenyl)-6-methyl-1-oxoethyl-3,4-dihydro-1*H*-[2,7]naphthylidine-2-yl]-acetic acid ethyl ester (200 mg, 0.584 mmol) and LiOH (37 mg, 0.876 mmol) were dissolved in a mixture of THF (6 ml) and distilled water (2 ml) and stirred for 1 hour at room temperature. The reaction solution was concentrated under reduced

pressure and dissolved in distilled water (20 ml). The solution was neutralized by adding a 1N-HCl aqueous solution at 0 °C, while stirring. The precipitated crystal was filtered under reduced pressureand dried in vacuum to obtain 125 mg (68%) of white solid.

^{1}H NMR (300 MHz, DMSO-d6) δ 2.50(s, 3H), 2.98(t, 2H, *J* =6.3Hz), 3.65(t, 2H, *J*=6.3Hz), 4.14(s, 2H), 7.10-7.16(m, 2H), 7.19(s, 1H), 7.41-7.46(m, 2H), 12.78(brs, 1H).

Example 166: Synthesis of 2-[1,3]dioxolane-2-yl-methyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro -2*H*-[2,7]naphthylidine-1-one

215 mg (81 %) of 2-[1,3]dioxolane-2-yl-methyl-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 122 except that 8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one (200 mg, 0.780 mmol) and 2-bromomethyl-1,3-dioxolane (0.12 ml, 1.170 mmol) were used instead of 2*H*-[2,7]naphthylidine-1-one and benzyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59(s, 3H), 2.95(t, 2H, *J*=6.3Hz), 3.69(d, 2H, *J*=4.5Hz), 3.74(t, 2H, *J*=6.3Hz), 3.85-4.01 (m, 4H), 5.03(t, 1H, *J*=4.5Hz), 6.97(s, 1H), 7.04-7.10(m, 2H), 7.44-7.49 (m, 2H).

Example 167: Synthesis of 2-(2-[1,3]dioxolane-2-yl-ethyl)-8-(4-fluorophenyl)-6-methyl-3,4-dihydro -2*H*-[2,7]naphthylidine-1-one

252 mg (91%) of 2-(2-[1,3]dioxolane-2-yl-ethyl)-8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-[2,7]naphthylidine-1-one was obtained in white solid using the same method as in Example 122 except that 8-(4-fluorophenyl)-6-methyl-3,4-dihydro-2*H*-

[2,7]naphthylidine-1-one (200 mg, 0.780 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (0.14 ml, 1.170 mmol) were used instead of 2*H*-[2,7]naphthylidine-1-one and benzyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94-2.01(m, 2H), 2.58(s, 3H), 2.94(t, 2H, *J*=6.3Hz), 3.61-3.66(m, 4H), 3.81-3.98(m, 4H), 4.91(t, 1H, *J*=4.5Hz), 6.96(s, 1H), 7.04-7.09(m, 2H), 7.43-7.48(m, 2H).

Example 168: Synthesis of 6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one Synthesis of

A column chromatography (20% EA/Hx) was performed on the byproduct obtained during the synthesis of 8-chloro-6-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one to obtain 1.40 g (26%) of white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06(s, 1H), d 4.44(t, J=6.0Hz, 2H), 3.82-3.73(m, 1H), 2.97(t, J=6.0Hz, 2H), 1.84-1.23(m, 10H).

Example 169: Synthesis of 2-methoxy-4-methyl-6-thiophene-2-yl-nicotinonitrile

2.68 g (84%) of 2-methoxy-4-methyl-6-thiophene-2-yl-nicotinonitrile was obtained in white solid using the same method as in Example 27 except that 6-chloro-2-methoxy-4-methyl-nicotinonitrile (2.52g, 13.81 mmol) was used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, 1H, J=1.0Hz, 3.6Hz), 7.47(dd, 1H, J=1.0, 3.6Hz), 7.16-7.12 (m, 2H), 4.10(s, 3H), 2.52(s, 3H).

Example 170: Synthesis of (3-cyano-2-methoxy-6-thiophene-2-yl-pyridine-4-yl)-acetic acid methyl ester

2.63 g (85%) of (3-cyano-2-methoxy-6-thiophene-2-yl-pyridine-4-yl)-acetic acid methyl ester was obtained in yellow solid using the same method as in Example 1 except that 2-methoxy-4-methyl-6-thiophene-2-yl-nicotinonitrile (2.41 g, 10.75 mmol) was used instead of 4-methyl-nicotinonitrile .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, J=1.1Hz, 3.6Hz, 1H), 7.49(dd, J=1.1, 3.6, 1H), 7.26(s, 1H) 7.16-7.12(m, 1H).

Example 171: Synthesis of 4-(2-hydroxyethyl)-2-methoxy-6-thiophene-2-yl-nicotinonitrile

1.87 g (88%) of 4-(2-hydroxyethyl)-2-methoxy-6-thiophene-2-yl-nicotinonitrile was obtained in light yellow solid using the same method as in Example 2 except that (3-cyano-2-methoxy-6-thiophene-2-yl-pyridine-4-yl)-acetic acid methyl ester (2.35 g, 8.14 mmol) was used instead of (3-cyano-pyridine-4-yl)-acetic acid methyl ester .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, 1H, J=1.2Hz, 3.9Hz) 7.48(dd, 1H, J=1.2Hz, 3.9Hz), 7.26(s, 1H), 7.13(dd, 1H, J=3.9Hz, 5.1Hz), 4.11(s, 3H), 4.00(t, J=6.2, 2H), 3.07(t, J=6.5H, 2H).

Example 172: Synthesis of 8-hydroxy-6-thiophene-2-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

8-hydroxy-6-thiophene-2-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (1.4g, 68%) was obtained in yellow solid using the same method as in Example 3 except

that 4-(2-hydroxy-ethyl)-2-methoxy-6-thiophene-2-yl-nicotinonitrile (2.06g, 7.91mmol) was used instead of 4-(2-hydroxy-ethyl)-nicotinonitrile .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74, 1H, dd J=1.1Hz, 3.6Hz), 7.52(dd, 1H, J=0.9Hz, 5.1Hz), 7.44(s, 1H), 7.14(dd, 1H, J=3.9Hz, 5.1Hz), 4.53(t, J=5.9Hz, 2H), 3.10(J=6.2Hz, 2H), 2.43(s, 3H).

Example 173: Synthesis of 6-ethyl-2-methoxy-4-methyl-nicotinonitrile

1.92 g (66%) of the target compound was obtained in light yellow oil using the same method as in Example 101 except that *n*-ethylmagnesium bromide (3M solution) was used instead of *n*-propyl magnesium bromide.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 4.00(s, 3H)2.69(q, J=7.5Hz, 2H), 2.44(s, 3H), 1.28(t, J=7.5Hz, 3H).

Example 174: Synthesis of (3-cyano-6-ethyl-2-methoxy-pyridine-4-yl)-acetic acid methyl ester

1.90 g (74%) of the target compound was obtained in colorless oil using the same method as in Example 1 except that 6-ethyl-2-methoxy-4-methyl-nicotinonitrile (1.92 g, 10.90 mmol) was used instead of 4-methyl-nicotinonitrile.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79(s, 1H), 4.06(s, 3H), 3.80(s, 2H), 3.76(s, 3H), 2.76(q, J=7.5Hz, 2H), 1.30(t, J=7.7Hz, 3H).

Example 175: Synthesis of 6-ethyl-4-(2- hydroxyethyl)-2-methoxy-nicotinonitrile

1.67g (100%) of the target compound was obtained in white solid using the same method as in Example 2 except that (3-cyano-6-ethyl-2-methoxy-pyridine-4-yl)-

acetic acid methyl ester (1.90g, 8.10 mmol) was used instead of(3-cyano-pyridine-4-yl)-acetic acid methyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27(s, 1H), 4.03(s, 3H), 3.95(t, J=J=6.3Hz, 2H), 3.01(t, J=6.5Hz, 2H), 2.74(q, J=7.6Hz, 2H), 1.29(t. J=7.7Hz, 3H).

Example 176: Synthesis of 6-ethyl-8-hydroxy-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

1.05 g (75%) of the target compound was obtained in white solid using the same method as in Example 3 except that 6-ethyl-4-(2-hydroxyethyl)-2- methoxy-nicotinonitrile (1.51g, 7.30 mmol) was used instead of 4-(2-hydroxyethyl)-nicotinonitrile.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09(s, 1H), 4.28(t, J=6Hz, 2H), 2.82(t, J=6.0Hz, 2H), 2.50(m, 2H), 1.16(t, J=7.4Hz, 3H).

Example 177: Synthesis of 6-ethyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl acetic acid ester

178 g (73%) of the target compound was obtained in white solid using the same method as in Example 21 except that 6-ethyl-8-hydroxy-3,4-dihydroxy-pyrano[3,4-c]pyridine-1-one (200 mg, 1.04 mmol) was used instead of 8-hydroxy-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04(s, 1H), 4.5 1(t, J=6Hz, 2H), 3.06(t, J=6Hz, 2H) 2.84(q, J=7.6Hz, 2H), 2.40(s, 3H), 1.32(t, J=7.7Hz, 3H).

Example 178: Synthesis of 8-chloro-6-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

822 mg (84%) of the target compound was obtained in white solid using the same method as in Example 90 except that 6-ethyl-8-hydroxy-3,4-dihydroxy-pyrano[3,4-c]pyridine-1-one (890 mg, 4.66 mmol) was used instead of 2,6-dihydroxy-4-methyl-nicotinonitrile.

1H NMR(300Hz, CDCl 3) δ 7.02(s, 1H), 4.48(t, J=5.9Hz, 2H), 3.05(t, J=5.9Hz, 2J) 2.84(q, J=7.6Hz, 2H), 1.32(t, J=7.8Hz, 3H).

Example 179: Synthesis of 6-ethyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

208 mg (100%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (170 mg, 0.80 mmol) and piperidine (0.16 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31(s, 1H), 4.40(t, J= 5.7Hz, 2H), 3.50(br s, 4H), 2.88(t, J=5.4Hz, 2H), 2.65(q, J=7.3Hz, 2H), 1.66(br s, 6H), 1.24(t, J=7.7Hz, 3H).

Example 180: Synthesis of 6-ethyl-8-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

524 mg (96%) of the target compound was obtained in white solid using the same method as in Example except that 8-chloro-6-ethyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (370 mg, 1.748 mmol) was used instead of 8-(4-methoxy-

benzylamino)-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and *p*-methoxybenzylamine (0.45 ml) was used instead of piperidine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48(br s, 1H), 7.31(d, J=9Hz, 1H), 6.87-6.82(m, 2H), 6.23(s, 1H), 4.71(d, J=6Hz, 2H), 4.43(t, J=6.0, 2H), 3.79(s, 3H), 2.87(t, J=6Hz, 2H), 2.65(q, J=7.5Hz, 2H), 1.26(t, J=7.5Hz, 3H).

Example 181: Synthesis of 8-amino-6-ethyl-3,4-dihydro-pyridine[3,4-c]pyridine-1-one

207 mg (96%) of the target compound was obtained in white solid using the same method as in Example 53 except that 6-ethyl-8-(4- methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (349 mg, 1.17 mmol) was used instead of 8-(4-methoxy-benzylamino)-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one .

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33(s, 1H), 4.46(t, J=6.2, 2H), 2.90(t, J=6Hz, 2H), 2.62(q, J=7.5Hz, 2H), 1.25(t, J=7.7Hz, 3H).

Example 182: Synthesis of 8-amino-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

191 mg (100%) of the target compound was obtained in white solid using the same method as in Example 53 except that 6-isopropyl-8-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (350 mg, 0.93nnol) was used instead of 8-(4-methoxy-benzylamino)-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one .

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33(s, 1H), 4.47(t, J=6.0Hz, 2H), 2.93-2.78(m, 3H), 1.24(d, J=6.9Hz, 6H).

Example 183: Synthesis of 6-isopropyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

204 mg (99%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (170 mg, 0.75 mmol) and piperidine (0.15 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.39(t, J=6.0Hz, 2H), 3.50(bs, 4H), 2.90-2.82(m, 3H), 1.65 (s, 6H) 1.24(d, J=6.9Hz, 6H).

Example 184: Synthesis of 8-[4-(2-hydroxyethyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

226 mg (87 %) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (180 mg, 0.80 mmol) and 2- piperazine-1-yl-ethanol (0.20 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.40(s, 1H), 3.68-3.57(m, 6H), 2.93-2.85(m, 3H), 2.67-2.60(m, 6H), 1.23(d, J=6.9Hz, 6H).

Example 185: Synthesis of 8-(4-benzyl-piperazine-1-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

289 mg (99%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-

pyrano[3,4-c]pyridine-1-one (180 mg, 0.80 mmol) and 1-benzylpiperazine (0.27ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25(m, 5H), 6.37(s, 1H), 4.39(t, J= 6.3Hz, 2H), 3.59-3.55(m, 6H), 2.91-2.81(m, 3H), 2.56(t, J=5.1Hz, 4H), 1.22(d, J=6.9Hz, 6H).

Example 186: Synthesis of 6-isopropyl-8-(4-phenyl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

254 mg (70%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (160 mg, 0.71 mmol) and 1-phenylpiperazine (0.22 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25(m, 2H), 6.94(d, J=8.4Hz, 2H), 6.86(t, J=7.1Hz, 1H), 6.42(s, 1H), 4.43(t, J=5.6Hz, 2H), 3.74(t, J=5.6Hz, 4H), 3.33(t, J=5.1Hz, 4H), 2.91-2.84(m, 3H), 1.25(d, J=7.2Hz, 6H)

Example 187: Synthesis of 8-[4-(2-ethoxy-phenyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

265 mg (99 %) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (150 mg, 0.66 mmol) and 1-(2-ethoxy-phenyl)-piperazine hydrochloride (322 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00-6.85(m, 4H), 6.39(s, 1H), 4.43(t, J=5.7, 2H), 4.10(q, J=7.0Hz, 2H), 3.76(t, J=4.8Hz, 4H), 3.21(t, J=4.8Hz, 4H), 2.93-2.84(m, 3H), 1.48(t, J=7.1Hz, 3H), 1.25(d, J=6.9Hz, 6H).

Example 188: Synthesis of 6-isopropyl-8-(4-methyl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

246 mg (96%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.89 mmol) and 4-methylpiperazine were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39(s, 1H), 4.41(t, J=5.9Hz, 2H), 3.60(t, J=5.1Hz, 4H), 2.94-2.82(m, 3H) 2.54(t, J=5.1Hz, 4H), 2.34(s, 3H), 1.23(d, J=6.3Hz, 6H).

Example 189: Synthesis of 6-isopropyl-8-morpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

239 mg (98%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.89 mmol) and morpholine (0.16 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34(s, 1H), 4.41(t, J= 5.6Hz, 2H), 3.47(br s, 4H), 2.93-2.85(m, 3H), 1.96-1,91(m, 4H), 1.25(d, J=6.9Hz, 6H).

Example 190: Synthesis of 6-isopropyl-8-pyrrolidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

227 mg (99%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.89 mmol) and pyrrolidine (0.15 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43(s, 1H), 4.42(t, J=5.6Hz, 2H), 3.82(t, J=4.8Hz, 4H), 3.56(t, J=4.7Hz, 4H), 2.94-2.86(m, 3H), 1.24(d, J=6.9Hz, 6H).

Example 191: Synthesis of 6-isopropyl-8-(methyl-phenethyl-amino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

260 mg (100%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (180 mg, 0.80 mmol) and methylphenylamine (0.23 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19(m, 5H), 6.34(s, 1H), 4.41(t, J=5.7Hz, 2H), 3.89-3.84(m, 2H), 3.03-2.86(m, 8H) , 1.28(d, J=6.9Hz, 6H).

Example 192: Synthesis of 8-[1,4']biperidinyl-1'-yl-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

271 mg (95%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-

pyrano[3,4-c]pyridine-1-one (180 mg, 0.80 mmol) and [1,4']biperidinyl (269 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47(s, 1H), 4.43(t, J=5.9Hz, 2H), 4.22(br s, 1H), 4.11(br s, 1H), 3.46-3.26(m, 3H), 3.02-2.82(m, 7H), 2.47-2.29(m, 4H), 2.05-1.85(m, 5H), 1.72-1.64(br s, 2H), 1.23(d, J=7.2Hz, 6H).

Example 193: Synthesis of 8-(4-benzyl-piperidine-1-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c] pyridine-1-one

280 mg (96%) of the target compound was obtained in white solid using the same method as in Example 353 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (180 mg, 0.80 mmol) and 4-benzylpiperidine (0.28 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.26(m, 2H), 7.21-7.15(m, 3H), 4.39(t, J=5.7Hz, 2H), 4.04(br d, J=13.5Hz, 2.99-2.81(m, 5H), 2.57(d, J=7.2Hz, 2H), 1.83-1.72(m, 3H), 1.46-1.33(m, 2H), 1.20(d, J=5.4Hz, 6H).

Example 194: Synthesis of 1-(6-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-3-carboxylamide

207 mg (82%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (180 mg, 0.80 mmol) and piperidine-3-carboxylamide

(205 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, DMSO d6) 7.3 1(br s, 1H), 6.83(br s, 1H) 6.55(s, 1H), 4.37(t, J=5.4Hz, 2H), 3,89(br d, J=12.9Hz), 2.99-2.79(m, 5H), 2.39-2.35(m, 1H), 1.89(m, 1H), 1.68-1.53(m 3H), 1.19(d, J=6.9Hz, 6H).

Example 195: Synthesis of 5-(-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-ylamino)-pentanoic acid

98 mg (36 %) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.89 mmol) and 5-aminopentanoic acid (208 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17(br s, 1H), 6.21(s, 1H), 4.44(t, J=6.2Hz, 2H), 3.61-3.55(m, 2H), 2.89-2.82(m, 3H), 2.42(t, J=7.1Hz, 2H), 1.76-1.69(m, 4H), 1.23(d, J=6.9Hz, 6H).

Example 196: Synthesis of 6-isopropyl-8-thiomorpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

259 mg (100%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.89 mmol) and thiomorpholine (0.17ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42(s, 1H) , 4.42(t, J=6.2Hz, 2H), 3.84-3.80(m, 4H), 2.93-2.86(m, 3H), 2.80-2.76(m, 4H), 1.23(d, J=6.9Hz, 6H).

Example 197: Synthesis of 8-(1,1-dioxoethyl-thiomorpholine-4-yl)-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

A mixture of 6-isopropyl-8-thiomorpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (280 mg, 0.96 mmol) and Oxone was dissolved in 4 ml of methanol. Then, 2 ml of water was added and the mixture was stirred for 3 hours. The reaction solution was diluted with water and extracted 3 times with MC. The organic layer was washed with saturated brine, dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. A column chromatography was performed with ethyl actate/hexane (1:1) on the resulting residue to obtain 210 mg (68%) of the target compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59(s, 1H), 4.46(t, J=5.7Hz, 2H), 4.01(t, J=5.3Hz, 4H), 3.24(t, J=5.3Hz, 4H), 3.00-2.87(m, 3H), 1.25(d, J=6.9Hz, 6H).

Example 198: Synthesis of 8-[4-(2-chlorophenyl)-piperazine-1-yl]-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

185 mg (90%) of the target compound was obtained in colorless oil using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (120 mg, 0.53 mmol) and 1-(2-chloro-phenyl)-piperazine hydrochloride (253 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-6.90 (m, 4H), 6.41 (s, 1H), 4.43 (t, J=6.0Hz, 2H), 3.73 (t, J=4.8Hz, 4H), 3.18 (t, J=4.8Hz, 4H), 2.93-2.84 (m, 3H), 1.25 (d, J=6.9Hz, 6H).

Example 199: Synthesis of 6-isopropyl-8-(4-pyridine-2-yl-piperazine-1-yl)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

178 mg (95%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (120 mg, 0.53 mmol) and 1-(2-pyridine)-piperazine (173 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20-8.18 (m, 1H), 7.51-7.45 (m, 1H), 6.64-6.59 (m, 2H), 6.42 (s, 1H), 4.43 (t, J=6.0Hz, 2H), 3.71 (s, 8H), 2.93-2.86 (m, 3H), 1.23 (d, J=6.9Hz, 6H).

Example 200: Synthesis of 1-(6-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-3-carboxylic acid ethyl ester

175 mg (95%) of the target compound was obtained in white solid using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (120 mg, 0.53 mmol) and piperidine-3-carboxylic acid ethyl ester (170 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (s, 1H), 4.43-4.39 (m, 2H), 4.28-4.22 (m, 1H), 4.14 (q, J=6.9Hz, 2H), 3.91-3.86 (m, 1H), 3.13-2.71 (m, 6H), 2.13-2.09 (m, 1H), 1.78-1.62 (m, 3H), 1.27-1.22 (m, 9H).

Example 201: Synthesis of 1-(6-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-8-yl)-piperidine-4-carboxylic acid ethyl ester

170 mg (92%) of the target compound was obtained in colorless oil using the same method as in Example 35 except that 8-chloro-6-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (120 mg, 0.53 mmol) and piperidine-4-carboxylic acid ethyl ester (170 mg) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.37 (s, 1H), 4.40 (t, J=6.3Hz, 2H), 4.14 (q, J=6.9Hz, 2H), 4.06-3.99 (m, 2H), 3.16-3.07 (m, 2H), 2.92-2.81 (m, 3H), 2.60-2.50 (m, 1H), 1.98-1.77 (m, 4H), 1.28-1.23 (m, 9H).

Example 202: Synthesis of 2-propyl-6-methoxy-4-methyl-nicotinonitrile

10.2 g (89%) of the target compound was obtained in light yellow oil using the same method as in Example 101 except that 2-chloro-6-methoxy-4-methyl-nicotinonitrile (11 g, 60.3 mmol) and propyl magnesium bromide (2 M solution) were used instead of 6-chloro-2- methoxy-4-methyl-nicotinonitrile and *n*-propyl magnesium bromide .

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47(s, 1H), 3.95(s, 3H), 2.89(t, J=4.7Hz, 2H), 2.44(s, 3H), 1.81(m, 2H), 1.00(t, J=7.4, 3H).

Example 203: Synthesis of (3-cyano-2-propyl-6-methoxy-pyridine-4-yl)-acetic acid methyl ester

10.47 g (79%) of the target compound was obtained in transparent oil using the same method as in Example 1 except that 2-propyl-6-methoxy-4-methyl-nicotinonitrile (10.15 g, 53.35 mmol) was used instead of 4-methyl-nicotinonitrile.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6. 58(s, 0.93), 3.97(s, 3H), 3.77(s, 2H), 3.75(s, 3H), 2.92(t, J=7.7Hz, 2H), 1.86-1.78(m, 2H), 1.01(t, J=7.4Hz, 3H).

Example 204: Synthesis of 4-(2-hydroxyethyl)-2-propyl-6-methoxy-nicotinonitrile

9.03g (97%) of the target compound was obtained in white solid using the same method as in Example 2 except that (3-cyano-2- propyl-6-methoxy-pyridine-4-yl)-acetic acid methyl ester (10.46 g, 42.13 mmol) was used instead of (3-cyano-pyridine-4-yl)-acetic acid methyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57(s, 1H), 3.97-3.93(m, 5H), 3.00(t, J=6.3Hz, 2H), 2.91(t, J=7.7Hz, 2H), 1.88-1.75(m, 2H), 1.01(t, J=7.4Hz, 3H).

Example 205: Synthesis of 6-hydroxy-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

7.94 g (94%) of the target compound was obtained in white solid using the same method as in Example 3 except that 4-(2-hydroxyethyl)-2-propyl-6-methoxy-nicotinonitrile (9.02 g, 40.95 mmol) was used instead of 4-(2-hydroxyethyl)-nicotinonitrile .

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.7(br s, 1H) 6.24(s, 1H), 4.39(t, J=5.7Hz, 2H), 3.13-3.08(m, 2H), 2.92-2.88(m, 2H), 1.82-1.70(m, 2H), 1.04(t, J=7.4Hz).

Example 206: Synthesis of 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

4.99 g (95%) of the target compound was obtained in white solid using the same method as in Example 90 except that 4-(2-hydroxyethyl)-2-propyl-6-methoxy-nicotinonitrile (4.83 mg, 23.37 mmol) was used instead of 2,6-dihydroxy-4-methyl-nicotinonitrile .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H), 4.46(t, J=6.0Hz, 2H), 3.23-3.18(m, 2H), 3.01(t, J=5.7Hz, 2H), 1.80-1.72(m, 2H), 1.02(t, J=7.4Hz, 3H).

Example 207: Synthesis of 6-piperidine-1-yl-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

Toluene (4.4 ml) and piperidine (0.18 ml) were added to 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.89 mmol) and heat refulx was performed overnight. The filtrate was concentrated under reduced pressure. A column chromatography was performed on the resulting residue with hexane-ethyl acetate (1:1) to obtain 243 mg (100%) of the target compound in white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (s, 1H), 4.34 (t, J=5.7Hz, 2H), 3.67 (t, J=5.7Hz, 4H), 3.10 (t, J=7.8Hz, 2H), 2.85 (t, J=5.7Hz, 2H), 1.81-1.58 (m, 8H), 0.999 (t, J=7.5Hz, 3H).

Example 208: Synthesis of 8-propyl-6-pyrrolidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

219 mg (95 %) of the target compound was obtained in white solid using the same method as in Example 207 except that pyrrolidine (0.15 ml) was used instead of piperidine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20(s, 1H), 4.35(t, J=5.4Hz, 2H), 3.68(t, J=5.4Hz, 4H), 3.11(t, J=7.7Hz, 2H), 2.86(t, J=5.9Hz, 2H), 1.81-1.59(m, 8H), 1.00(t, J=7.4Hz, 3H).

Example 209: Synthesis of 6-morpholine-4-yl-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

157 mg (64%) of the target compound was obtained in white solid using the same method as in Example 207 except that morpholine (0.15 ml) was used instead of piperidine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20(s, 1H), 4.37(t, J=5.9Hz, 2H), 3.80 (t, J=4.8Hz, 4H), 3.67(t, J=5.0Hz, 4H), 3.1(t, J=7.7Hz, 2H), 2.89(t, J=5.7Hz, 2H), 1.81-1.68(m, 2 H), 1.00(t, J=7.4Hz, 3H).

Example 210: Synthesis of 6-(4-methoxybenzylamino)-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

NMP (11 ml), triethylamine (0.93 ml) and 4-methoxybenzylamine (0.58 ml) were added in sequence to 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (500 mg, 2.21 mmol) and heat reflux was performed overnight. A saturated ammonium chlrodie solution was added to the reaction solution. The resulting neutralized solution was extracted with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride solution, dired with anhydrous sodium sulfate and filtered. The remainig solution was concentrated under reduced

pressure. A column chromatography was performed on the resulting residue with hexane-ethyl acetate (1:1) to obtain 636 mg (88%) of the target compound in white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26(m, 2H), 6.88(m, 2H), 6.00(s, 1H), 5.27(br s, 1H), 4.46(d, J=5.7Hz, 2H), 4.35(t, J=5.9Hz, 2H), 3.81(s, 3H), 3.11-3.07(m, 2H), 2.84(t, J=6.0Hz, 2H), 1.79-1.67(m, 2H), 1.00(t, J=7.4Hz, 3H).

Example 211: Synthesis of 6-amino-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

208 mg (94%) of the target compound was obtained in white solid using the same method as in Example 53 except that 6-(4-methoxy-benzylamino)-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (350 mg, 1.07 mmol) was used instead of 8-(4-methoxy- benzylamino)-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14(s, 1H), 4.83(br s, 2H), 4.37(t, J=6.0Hz, 2H), 3.10-3.05(m, 2H), 2.87(t, J=5.9Hz, 2H), 1.11-1.65(m, 2H), 1.01(t, J=7.4Hz, 3H).

Example 212: Synthesis of 8-cyclohexyl-6-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

227 mg (97%) of the target compound was obtained in white solid using the same method as in Example 207 except that 6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (198 mg, 0.74 mmol) was used instead of 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one .

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17(s, 1H), 4.33(t, J=6.0Hz, 2H), 3.83-3.66(m, 5 H), 2.84(t, J=5.7Hz, 2H), 1.85-1.23(m, 16H).

Example 213: Synthesis of 8-cyclohexyl-6-morpholine-4-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

220 mg (89 %) of the target compound was obtained in white solid using the same method as in Example 207 except that 6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (208 mg, 0.78 mmol) and morpholine (1.36 ml) were used insated of 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and piperidine.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18(s, 1H), 4.35(t, J=5.9Hz, 2H), 3.83-3.66(m, 9H), 2.88(t, J=5.9Hz, 2H), 1.85-1.23(m, 10H).

Example 214: Synthesis of 8-cyclohexyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

555 mg (81%) of the target compound was obtained in white solid using the same method as in Example 210 except that 6-chloro-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (500 mg, 1.88 mmol) was used instead of 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.91-6.86(m, 2H), 5.96(s, 1H)5.15(br s, 1H), 4. 49(d, J=6.0Hz, 2H), 4.3 3(t, J=5.9Hz, 2H), 3.86-3.74(m, 5H), 2.82(t, J=5.1Hz, 2H), 1.82-1.18(m, 10H).

Example 215: Synthesis of 6-amino-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

244 mg (92%) of the target compound was obtained in white solid using the same method as in Example 53 except that 6-(4-methoxy-benzylamino)-8-cyclohexyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (398 mg, 1.09mol) was used instead of 8-(4-methoxy- benzylamino)-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10(s, 1H), 4.72(br s, 1H), 4.35(t, J=5.9Hz, 2H), 3.78(t, J=11.0Hz, 1H), 2.85(t, J=6.0Hz, 2H), 1.81-1.25(m, 10H).

Example 216: Synthesis of 6-chloro-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

The byproduct formed during the synthesis in Example 183 was separated by column chromatography.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06(s, 1H), d 4.44(t, J=6.0Hz, 2H), 3.82-3.73(m, 1H), 2.97(t, J=6.0Hz, 2H), 1.23(d, J=6.3Hz, 6H).

Example 217: Synthesis of 8-isopropyl-6-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

238 mg (98%) of the target compound was obtained in white solid using the same method as in Example 207 except that 6-chloro-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.89 mmol) was used instead of 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29(s, 1H), 6.89(m, 2H), 5.98(s, 1H), 5.17(br s, 1H), 4.51(d, J=5.4Hz, 2H), 4.34(t, J=6.1Hz, 2H), 4.19-4.10(m, 1H), 8.81 (s, 3H), 2.83(t, J=5.7Hz, 2H), 1.23(d, J=6.3Hz, 6H).

Example 218: Synthesis of 8-isopropyl-6-(4-methoxybenzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

567 mg (78%) of the target compound was obtained in white solid using the same method as in Example 210 except that 8-chloro-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (500 mg, 2.22 mmol) was used instead of 6-chloro-8-propyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.91-6.87(m, 2H), 5.98(s, 1H) , 5.17(br s, 1H), 4. 51(d, J=5.4Hz, 2H), 4.34(t, J=5.9Hz, 2H), 4.18- 4.10(m, 1H), 3.81(s, 3H), 2.83 (t, J=5.7Hz, 2H), 1.23(d, J=6.3Hz, 3H).

Example 219: Synthesis of 6-amino-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

226 mg (86 %) of the target compound was obtained in white solid using the same method as in Example 53 except that 8-isopropyl-6-(4-methoxy-benzylamino)-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (416 mg, 1.27mol) was used instead of8-(4-methoxy-benzylamino)-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02(s, 1H), 4.91(br s, 1H), 4.42(t, J=5.9Hz, 2H), 4.23-4.18(m, 1H), 2.93(t, J=5.7Hz, 2H), 1.27(d, J=6.3Hz, 3H).

Example 220: Synthesis of N-(8-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide

To an acetonitrile (3.6nl) solution containing 6-amino-8-isopropyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (150 mg, 0.73 mmol) were added benzenesulfonyl chloride (0.39ml) and pyridine (0.24 ml). The mixture was

stirred overnight at 50 °C. The reaction solution was neutralized with a saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. A column chromatography was performed on the resulting residue with hexane-ethyl acetate (1:1) to obtain 226 mg (89 %) of the target compound in white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H), 7.60-7.47(m, 3H), 6.71(s, 1H), 4.40(t, J=5.9Hz, 2 H), 4.27-4.20(m, 1H), 2.94(t, J=5.9Hz, 2H), 1.29(d, J=6.9Hz, 6H).

Example 221: Synthesis of 4-fluoro-N-(8-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide

244 mg (92%) of the target compound was obtained in white solid using the same method as in Example 220 except that 4-fluorobenzenesulfonyl chloride (424 mg) was used instead of benzenesulfonyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00-7.95 (m, 2H), 7.20-7.14(m, 2H), 6.68(s, 1H), 4.43-4.26(m, 3H), 2.95(t, J=6.2Hz, 2H), 1.30(d, J=6.9Hz, 6H).

Example 222: Synthesis of 4-chloro-N-(8-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-benzenesulfonamide

222 mg (80 %) of the target compound was obtained in white solid using the same method as in Example 220 except that 4-chlorobenzenesulfonyl chloride (309 mg) was used instead of benzenesulfonyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.87 (m, 2H), 7.49-7.26(m, 2H), 6.67(s, 1H), 4.42-4.27(m, 3H), 2.95(t, J=6.0Hz, 2H), 1.31(d, J=6.9Hz, 6H).

Example 223: Synthesis of N-(8-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-methoxy-benzenesulfonamide

244 mg (73%) of the target compound was obtained in white solid using the same method as in Example 220 except that 4-methoxysulfonyl chloride (450 mg) was used instead of benzenesulfonyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.86 (m, 2H), 6.99-6.94(m, 2H), 6.74(s, 1H), 4.39(t, J=5.9Hz, 2H), 4.23-4.13(m, 1H), 2.93(t, J=5.7Hz, 2H), 1.26 (d, J=6.6Hz, 6H).

Example 224: Synthesis of N-(8-isopropyl-1-oxoethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridine-6-yl)-4-methyl-benzenesulfonamide

203 mg (78%) of the target compound was obtained in white solid using the same method as in Example 220 except that 4-methylsulfonyl chloride (277 mg) was used instead of benzenesulfonyl chloride.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 -7.82 (m, 2H), 7.31 -7.28(m, 2 H), 6.74(s, 1H), 4.39 (t, J=5.9Hz, 2H), 4.27-4.20(m, 1H), 2.93 (t, J=5.7Hz, 2H), 2.41(s, 3H), 1.27 (d, J=6.9Hz, 6H).

Example 225: Synthesis of 6-*tert*-butyl-2-hydroxy-4-methyl-nicotinonitrile

To an ethanol solution containing 5,5-dimethyl-hexane-2,4-dione (6 g, 42.19 mmol) and 2-cyanoacetamide was added piperidine (5.0 ml) and heat flux was performed for 3 days. The reaction solution was slowly poured to 200 ml of a 1M

hydrochloric acid solution and kept in a refrigerator. The resulting solid was filtered and dried in vacuum to obtain 7.30 g (91%) of the target compound in white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.0 (s, 1H), 6.21 (s, 1H), 2.34 (s, 3H), 1.25 (s, 9H).

Example 226: Synthesis of 6-*tert*-butyl-2-chloro-4-methyl-nicotinonitrile

7.53 g (96%) of the target compound was obtained in white solid using the same method as in Example 90 except that 5-*tert*-butyl-2-hydroxy-4-methyl-nicotinonitrile (7.20g, 37.8 mmol) was used instead of 2,6-dihydroxy-4-methyl-nicotinonitrile .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (s, 1H), 2.55 (s, 3H), 1.34 (s, 9H).

Example 227: Synthesis of (6-*tert*-butyl-2-chloro-3-cyano-pyridine-4-yl)-acetic acid methyl ester

5.01 g (82%) of the target compound was obtained in colorless oil using the same method as in Example 1 except that 6-tert-2-butyl-2-chloro-4-methyl-nicotinonitrile (4.66 g, 22.85 mmol) was used instead of 4-methyl-nicotinonitrile.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 3.87 (s, 2H), 3.77 (s, 3H), 1.35 (s, 9H).

Example 228: Synthesis of 6-*tert*-butyl-2-chloro-4-(2-hydroxyethyl)-nicotinonitrile

4.21g (94%) of the target compound was obtained in colorless oil using the same method as in Example 2 except that (6-*tert*-butyl-2- chloro-3-cyano-pyridine-4-

yl)-acetic acid methyl ester (5 g, 18.74 mmol) was used instead of (3-cyano-pyridine-4-yl)-acetic acid methyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 3.98 (t, J=6.3Hz, 2H), 3.08 (t, J=6.0Hz, 2H), 1.36 (s, 9H).

Example 229: Synthesis of 6-*tert*-butyl-8-hydroxy-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

2.53 g (68%) of the target compound was obtained in white solid using the same method as in Example 3 except that 5-*tert*-butyl-2-chloro-4-(2-hydroxyethyl)-nicotinonitrile (4.0g, 7.27 mmol) was used instead of 4-(2-hydroxyethyl)-nicotinonitrile.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (s, 1H), 4.31 (t, J=6.0Hz, 2H), 2.88 (t, J=6.0Hz, 2H), 1.28 (s, 9H).

Example 230: Synthesis of 6-*tert*-butyl-8-chloro-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

2.73 g (100%) of the target compound was obtained in white solid using the same method as in Example 90 except that 6-*tert*-butyl-8-hydroxy-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (2.53 g, 11.38 mmol) was used instead of 2,6-dihydroxy-4-methyl-nicotinonitrile .

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 4.48 (t, J=5.7Hz, 2H), 3.07 (t, J=6.0Hz, 2H), 1.36 (s, 9H).

Example 231: Synthesis of 6-*tert*-butyl-8-piperidine-1-yl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one

239 mg (100%) of the target compound was obtained in white solid using the same method as in Example 35 except that 6-*tert*-butyl-8-chloro-3,4-dihydro-pyrano[3,4-c]pyridine-1-one (200 mg, 0.83 mmol) and piperidine (0.16 ml) were used instead of 8-chloro-6-methyl-3,4-dihydro-pyrano[3,4-c]pyridine-1-one and 4-fluoroaniline .

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (s, 1H), 4.40 (t, J=5.7Hz, 2H), 3.51 (bs, 4H), 2.89 (t, J=5.7Hz, 2H), 1.65 (s, 6H), 1.29 (s, 9H).

Meanwhile, the compounds of the above formula 1 of the present invention can be manufactured in various forms of preparations depending on purposes. The followings are only a few of exemplary methods manufacturing preparations comprising the compounds of the above formula 1 as an active component and therefore it should not be construed as limiting the scope of this invention.

Preparation 1 : Production of tablets (Direct Compression)

5.0 mg of active component was sieved and then mixed with 14.1 mg of lactose, 0.8 mg of Crospovidone USNF and 0.1 mg of magnesium stearate. The mixture was pressed and prepared in tablets.

human whole blood over to those of Indomethacin, a commercially available anti-inflammatory and analgesic agent, in particular, about two to three times greater in inhibitory activities on its production of TNF-α and IL-1α. Further, the compound of Example 9 showed a similar level of inhibitory activity to that of Indomethancin on the production of PGE_2.

2) Cytokine inhibitory activity in animal model

Sprague Dawley (SD) rats with body weights of about 180 to about 200 g were fasted (free drinking) and then tested. Test compounds were administered orally at 40 mg/kg and then abdominally administered with LPS 1 mg/kg after 1 hour. After 2 hours, the rats were sacrificed and bloods wre collected from abdominal vein, stored at room temperature for about 2 hours, and then centrifuged at 12,000 rpm for about 2 minutes. Thus produced plasma was respectively collected and its TNF-α in each plasma was quantitated using mouse TNF-α ELISA kit based on the amount of recombinant TNF-α in rats. The plate used was coated with anti-rat TNF-α monoclone IgG antibodies. Likewise, for the test of IL-1α, IL-1α in each plasma was quantitated using the above plasma and mouse IL-1α ELISA kit based on the amount of recombinant IL-1α in rats. The plate used was coated with anti-rat IL-1α monoclone IgG antibodies. Further, for the test of IL-6, IL-6 in each plasma was quantitated using the above plasma and mouse IL-6 ELISA kit based on the amount of recombinant IL-6 in rats. Further, for the test of INF-γ, INF-γ in each plasma was quantitated using the above plasma and mouse INF-γ ELISA kit based on the amount of recombinant INF-γ in rats. The plate used was coated with anti-rat INF-γ monoclone IgG antibodies. From the above tests, inhibitory rates on the

Table 2

Test compound	TNF-α Inhibition Rate (Conc.)
Indomethacin	46 % (200 mg/kg)
Compound of Ex. 3	75 % (40 mg/kg)
Compound of Ex. 6	39 % (40 mg/kg)
Compound of Ex. 9	59 % (40 mg/kg)
Compound of Ex. 21	93 % (40 mg/kg)
Compound of Ex. 30	79 % (40 mg/kg)
Compound of Ex. 32	74 % (40 mg/kg)
Compound of Ex. 33	90 % (40 mg/kg)
Compound of Ex. 53	53 % (40 mg/kg)
Compound of Ex. 77	66 % (40 mg/kg)
Compound of Ex. 78	68 % (40 mg/kg)
Compound of Ex. 79	78 % (40 mg/kg)
Compound of Ex. 115	43 % (40 mg/kg)
Compound of Ex. 117	69 % (40 mg/kg)

Test compound	Treatment	TNF-α Inhibition Rate (%)
Compound of Ex. 126	10 mg/kg	99
Compound of Ex. 133	10 mg/kg	31
Compound of Ex. 135	10 mg/kg	54
Compound of Ex. 146	10 mg/kg	99
Compound of Ex. 154	3 mg/kg	27
Compound of Ex. 156	3 mg/kg	57

Compound of Ex. 158	3 mg/kg	97
Compound of Ex. 179	10 mg/kg	85
Compound of Ex. 183	10 mg/kg	97
Compound of Ex. 207	3 mg/kg	22
BIRB-796	3 mg/kg	0
	10 mg/kg	30

Table 3

Test compound	IL-α Inhibition rate (conc.)	IL-6 Inhibition rate (conc.)	INF-γ Inhibition rate (conc.)
Indomethacin	24 % (200 mg/kg)	60 % (200 mg/kg)	13 % (200 mg/kg)
Compound of Ex. 3	65 % (40 mg/kg)	71 % (40 mg/kg)	48% (40 mg/kg)
Compound of Ex. 6	52 % (40 mg/kg)	78 % (40 mg/kg)	51 % (40 mg/kg)
Compound of Ex. 9	62 % (40 mg/kg)	43.% (40 mg/kg)	45 % (40 mg/kg)

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As shown in the above tables 2 and 3, the pyridine compounds prepared according to the present invention, showed superiorities in cytokine inhibition activities in rat model over to those of Indomethacin, in particular, about at least two times greater in inhibitory activities on its production of TNF-α, IL-α, IL-6 and INF-γ. Further, the compounds of Examples 21, 30, 32, 33, and 79 showed a 1.5 or 2 times greater inhibitory activities compared to that of Indomethancin on the production of TNF-α. Further, the compounds of Examples 126, 146, 158 and 183 showed much superior activity to BIRB-796, known as an orally administered TNF-α inhibitor.

3) Cytokine inhibitory activity in cells

General reagents used were purchased from Sigma-Aldrich chem. Co. and cytokine inhibitory activities were tested as follows. Mediums and reagents used in cell culture were purchased from GIBCO BRL (USA), and mouse TNF-α ELISA kit was purchased from R&D system (USA). The apparatus used ELISA reader (Spectra max-Plus 384, Molecular Device, USA).

Murine macrophage cell line RAW 264.7 was kindly provided by Korean Tissue Culture Center (KTCC). The cell line was cultured in DMEM medium containing 10% FBS, in a cell culturing device at the condition of 37 °C, 5% CO_2. First, murine RAW 264.7 was cultured cultured in DMEM medium containing 10% FBS for about 24 hours, and cells were planted 200 μL each in 96 well plates at the concentration of 5×10^5/mLand cultured for about 24 hours. Then, test compounds were treated at various concentrations and then reacted at 37 °C for about 1 hour, wherein 1 μg/mL of lipopolysaccharide (LPS) was added thereto and reacted at

37 °C for about 12 hours. The supernatant was recovered and the amount of murine TNF-α on the medium was quantitated using ELISA kit. Thalidomide was